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09/745,920	12/21/2000	Kenneth C. Parker	SYP-155 7783/571	2871

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EXAMINER	
SMITH, CAROLYN L	
ART UNIT	**PAPER NUMBER**
1631	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/745,920	PARKER, KENNETH C.	
	Examiner	Art Unit	
	Carolyn L Smith	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *30-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-33* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All *b)*☐ Some * *c)*☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

Applicant's election of Group I (claims 1-29) in Paper No. 7, filed 12/23/02, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 30-33 are withdrawn from consideration as being drawn to a non-elected Group.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The present title is directed to methods and apparatus for mass fingerprinting of biomolecules whereas in contrast the elected claims include only methods and an article of manufacture for mass fingerprinting of biomolecules.

Claims herein under examination are 1-29.

Specification

The disclosure is objected to because of the following informalities: "haveone" lacks a space in between the words on page 43, line 14, and the presence of a double period on page 52, line 5. Appropriate correction of these and any other spelling or grammatical errors is requested.

Claims Rejected Under 35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claim 23 is vague and indefinite due to the unclarity of citing an abbreviation, such as MS-MS, on line 19. Correction is suggested by amending in of the full name in parentheses. Claims 24-27 and 29 are also rejected due to their direct or indirect dependence from claim 23.

Claims 1 (lines 3, 12, and 21), 2 (lines 1 and 8), 8 (line 3), 11 (line 12), 12 (lines 1 and 6), 13 (lines 1 and 10), 14 (lines 1 and 8), 17 (line 10), 18 (line 7), 19 (line 13), 21 (lines 1 and 2), 23 (lines 1 and 10), and 25 (line 3) recite the terms "likelihood" and "likely" which are vague and indefinite. It is unclear to what extent or degree these terms "likelihood" and "likely" entail in these particular claims. For example, the mere mention of something being not likely, likely, strongly likely, or other degrees of "likely" does not adequately define the true meaning of any of these terms. Clarification of the metes and bounds of these claims via clearer wording is requested. Claim 3-7, 9-10, 15-16, 20, 22, 24, and 26-29 are also rejected due to its dependency from claims 1, 8, 14, 19, 23, and 25.

Claims 12 and 14 recite the phrase "minimum number" which is vague and indefinite. It is unclear to what the "minimum number" is referring. One interpretation of "minimum number" could be a number randomly selected by the researcher. Another interpretation of "minimum number" could be a predetermined cut-off value based on statistical principles. Clarification of the intended meaning of this phrase via clearer claim wording is requested. Claim 15 is also rejected due to its dependency from claim 14.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 4, 7, 21-24, and 28-29 are rejected under 35 U.S.C. 102(a) as being anticipated by Yates, III et al. (P/N 6,017,693).

Yates, III et al. disclose a method of using tandem mass spectrometry to determine sequences which are likely to be identical to an experimentally derived peptide (col. 2, lines 22-27). Yates, III et al. disclose introducing an unknown peptide into a first mass spectrometer to separate it from the rest of the sample (col. 2, lines 54-64). The peptide and its fragments are then passed through a second mass spectrometer to obtain an intensity and mass-to-charge ratio (m/z) (col. 3, lines 4-7), which includes mass signals as seen in Figure 5 (col. 3, lines 7-9). Yates, III et al. disclose a method in Figure 2 where an unknown (12) is analyzed in a tandem mass spectrometer (14) to obtain fragment spectrum (16) and compared (24) to the mass spectra (22) of proteins from a protein sequence library (20) on a computer. Yates, III et al. disclose performing this comparison and calculating a closeness-of-fit measure or score for each of a plurality of mass spectra (col. 4, lines 9-16). Yates, III et al. disclose determining if a fragment mass is found in a measured fragment spectrum and scores are generated and sorted in a repeated cycle which results in one or more candidate amino acid sequences (col. 3, lines 21-28). Yates, III et al. disclose high-scoring candidate sequences (col. 3, lines 29-30). Yates, III et al. disclose a mass tolerance of the unknown peptide from which spectra from known sequences are

identified if they fall within this tolerance amount (col. 4, lines 59-67 and Figure 4) which is reasonably interpreted as the biological fragment detection parameter. Yates, III et al. disclose an example using a tolerance of +0.05% of the mass of the unknown peptide used (col. 5, lines 25-26) which is reasonably interpreted as a detection efficiency as stated in claims 7 and 24. Yates, III et al. disclose the high probability or likelihood that the unknown peptide has an identical amino acid sequence to one of the subsequences taken from the protein sequence library due to the high closeness-of-fit score with respect to the spectra comparison (col. 4, lines 16-23). Yates, III et al. further disclose the high probability of the unknown protein and the known protein from the library as being identical or similar with subsequences with high closeness-of-fit scores (col. 4, lines 23-29). Yates, III et al. disclose performing further MS-MS analysis if original scoring procedures do not delineate an answer of protein match (col. 8, lines 53-61) as stated in claim 23.

Yates, III et al. disclose the calculation of closeness-of-fit (56) in Figure 3 and then the selection of sequences with the highest scores (58). Yates, III et al. disclose outputting matching data for sequences with the highest correlation function (62).

Yates, III et al. disclose normalizing the spectrum (col. 4, lines 35-38) which is reasonably interpreted as a form of calibration as in instant claim 4.

Yates, III et al. disclose the above-mentioned procedure as being performed automatically on a computer (col. 4, lines 30-34). Yates, III et al. disclose computational resources and storage facilities (col. 9, lines 24-49 and col. 21, lines 8-10) as stated in claims 28 and 29.

Thus, Yates, III et al. teach all of the limitations of claims 1, 4, 7, 21-24, and 28-29.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 11-17, 21-24, and 28-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yates, III et al. (P/N 6,017,693), in view of Gras et al. (Electrophoresis 1999, Volume 20) and Wright et al. (P/N 5,710,713).

Yates, III et al. as noted above in the 102 rejection teach the limitations of claims 1, 2, 4, 7, 21-24, and 28-29. Yates, III et al. describe identifying 200 of the most intense ions from the experimentally-derived fragment spectrum (col. 4, lines 44-45) as mentioned in claim 14. Yates, III et al. describee the calculation of closeness-of-fit (56) in Figure 3 and then the selection of sequences with the highest scores (58). Yates, III et al. describe outputting matching data for sequences with the highest correlation function (62) which suggests that any scores lower than the highest scores are likely absent and therefore are not outputted (also see Figure 6D) as stated in claim 2. Yates, III et al. do not teach correcting a mass intensity for an isotopic variant (claim 3), removing noise (claim 5), removing artificial background intensity (claim 6), weighted biomolecule scores, fragment counts, and signal intensity scores to determine the likelihood of the presence or absence of a biomolecule as well as determining a relative concentration based on the biomolecule score.

Gras et al. describe a program that identifies a protein based on mass spectra despite chemical modifications (abstract, lines 1-5) which could be an isotopic variant as stated in claim 3. Gras et al. also describe this determination of isotopic variants via software that often comes with the spectrometer (page 3538, col. 1, lines 1-5 and col. 1, third paragraph). Gras et al. describe a trend or baseline as the signal produced if no material entered the mass spectrometer and in the absence of noise (page 3537, col. 2, lines 10-14; page 3538, col. 1, lines 18-24; and Figure 1) which is reasonably interpreted as the removal of noise and background intensity as stated in claims 5 and 6. Gras et al. describe the smoothing out of error functions related to the mass signals (page 3538, lines 21-26). Gras et al. describe using selected parameters to search proteins in a database that match the experimental spectra and assigning a score to the candidate protein (page 3541, col. 1, paragraph 2). Gras et al. describe the parameters' effects on the quality and efficiency of the identification (page 3541, col. 1, paragraph 3) as mentioned in claims 7 and 24. Gras et al. describe parameters that include the maximum distance between experimental and theoretical masses, the minimum number (or score) of matched peptides necessary for a protein to be selected, and the number of peaks returned by the peak detection program (page 3541, col. 1, paragraph 4). Gras et al. describe eliminating the least likely proteins in the list of candidates using parameters such as the minimum number of matched peptides or number of detected peaks, as well as depending on their thresholds (page 3541, col. 2, paragraph 1). Gras et al. describe the parameter of peak intensity in the mass spectrum as well (page 3542, col. 2, lines 40-44). Gras et al. describe a mass level parameter which characterizes the degree of match between the experimental mass and the peptide mass of the search library protein (page 3541, col. 1, paragraph 3) which is reasonably interpreted as a mass error. Gras et

al. describe defining score calculations by determining the most important parameters, their relative weights and how to integrate them all into the score calculation (page 3542, col. 2, lines 20-23). Gras et al. describe counting the number of experimental masses matching theoretical peptide masses (page 3542, col. 2, lines 29-33) which are fragment counts. Gras et al. describe the concept of the more identified masses a protein has in the mass spectrum, the higher is the confidence for its identification (page 3542, col. 2, lines 33-35). Gras et al. describe assigning weights to each peptide mass, depending on the presence of a match resulting in a score calculation (page 3542, col. 2, lines 36-41 and page 3543, col. 2, lines 15-19). Gras et al. describe taking into account the calibration error of the measuring device, eliminating masses that are too far from the regression line, and repeating this process when the previous no masses were eliminated in the previous step (page 3543, col. 1, paragraph 3). Gras et al. describe identifying proteins via scores obtained of the proteins in a ranked list of candidate proteins (page 3543, col. 2, lines 37-41).

Wright et al. describe the concentration in the mass spectrometer, its use in standardization of the process including relative estimates, and relative errors resulting without a calibration correction (col. 17, lines 6-26) as stated in claim 16.

Yates, III et al. state that interpretation of the fragment spectra so as to produce candidate amino acid sequences is time-consuming, often inaccurate, and highly technical (col. 1, lines 52-59). Yates, III et al. note that relying on human interpretation often means that analysis is relatively slow and lacks strict objectivity (col. 1, lines 59-60). They further state that approaches based on peptide mass mapping are limited to peptide masses derived from an intact homogeneous protein generated by specific and known proteolytic cleavage (col. 1, lines 61-64).

Yates, III et al. state that it would be useful to provide a system for correlating fragment spectra with known protein sequences in a fast and objective way (col. 1, lines 65-67). Yates, III et al. invented a spectral interpreting method that could be used with any size peptide (col. 20, lines 59-60). However, Yates, III et al. note that certain variations and modifications could be made to their invention. A skilled artisan in the art would have been motivated to make further improvements to the identification method of spectral data, such as that stated by Yates, III et al. (col. 2, lines 5-27) in order to provide more accurate results as stated by Yates, III et al. (col. 1, lines 52-59). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to include features such as correcting a mass intensity for an isotopic variant, removing noise and artificial background intensity, creating weighted biomolecule scores, fragment counts, and signal intensity scores to determine the likelihood of the presence or absence of a biomolecule, as stated by Gras et al., as well as determining a relative concentration based on the biomolecule score, as stated by Wright et al., in order to provide precise and fast determination of peptide masses, even if the peaks are of low intensity and overlap (Gras et al., abstract, lines 6-7) and to provide accurate and precise concentration estimates (Wright et al., col. 17, lines 19-21) to create more accurate results in mass spectral identification, as stated by Yates, III et al. (col. 1, lines 52-59).

Thus, Yates, III et al., in view of Gras et al. and Wright et al. motivate the limitations of claims 1-7, 11-17, 21-24, and 28-29.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (703) 308-6043. The examiner can normally be reached Monday through Friday from 8 A.M. to 4:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

March 7, 2003

ARDIN H. MARSCHEL
PRIMARY EXAMINER